A Phase I and Pharmacokinetic Trial of Erlotinib in Combination with Weekly Docetaxel in Patients with Taxane-Naive Malignancies

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Abstract

Purpose: This study aimed to define the maximum tolerated dose of weekly docetaxel combined with daily erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor.

Experimental Design: Patients with any solid tumor received 150 mg erlotinib with escalating doses of docetaxel (20, 25, 30, and 35 mg/m^2) on days 1, 8, and 15 every 28 days. The pharmacokinetics of docetaxel and erlotinib was determined on cycle 2, day 1. Erlotinib was given for a maximum of 12 cycles and docetaxel was given for up to 6 cycles.

Results: Twenty-five patients (17 males and 8 females) were enrolled with a median age of 56 years (range, 34-76); Eastern Cooperative Oncology Group performance status of 0/1 was 20/5. One patient had a dose-limiting toxicity in cycle 1 at the 25 mg/m^2 level (grade 3 enterocolitis). At 35 mg/m^2 docetaxel dose level, 6 of 10 patients required dose reductions to 30 mg/m^2 beyond cycle 1 due to neutropenia (3 patients) and mucositis, increased bilirubin, and diarrhea (1 patient each). The clearance of docetaxel and erlotinib of 61.7 and 8.16 L/h, respectively, did not seem to differ from historical controls. Responses were seen in non–small cell lung cancer, prostate cancer, and hepatobiliary cancers, including a complete response lasting 36+ months in a patient with hepatocellular carcinoma.

Conclusion: Although no maximum tolerated dose was reached in cycle 1 with 35 mg/m^2 docetaxel, repetitive dosing proved intolerable in a substantial number of patients; thus, the recommended phase II dose of weekly docetaxel is 30 mg/m^2 when combined with 150 mg of daily erlotinib.

The epidermal growth factor receptor (EGFR) is overexpressed and associated with a poor prognosis in many cancers (1–8). Several lines of evidence support the deleterious effects associated with EGFR overexpression, both via activation of the Ras-mitogen-activated protein kinase–mediated cell proliferation (9), inhibition of apoptosis via phosphatidylinositol 3-kinase-Akt and mammalian target of rapamycin pathway (9), as well as promoting cell survival by inducing vascular endothelial growth factor expression and angiogenesis (10, 11).

Erlotinib (Tarceva, OSI-774; OSI Pharmaceuticals) is an orally active reversible inhibitor of the EGFR tyrosine kinase enzyme that blocks cell cycle progression in the G_1 phase. Erlotinib inhibits the tyrosine kinase activity with an IC_{50} of 2 nmol/L and decreases EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nmol/L. Erlotinib confers a survival advantage and is approved for clinical use in the United States as a single agent in non–small cell lung cancer (12) and in combination with gemcitabine for pancreatic cancer (13). Taxanes are cytotoxic agents that bind to tubulin and prevent microtubule disassembly. Docetaxel has also been found to inhibit angiogenesis and induce apoptosis in both *in vitro* and *in vivo* models, and most importantly, it has been shown to have clinical activity in numerous tumor types (14–17). Preclinical data showed that EGFR inhibition in combination with docetaxel conferred increased antiproliferative and cytotoxic effects in various cancer cell lines and tumor models (18–20). Prior phase I studies tested docetaxel administered every 3 weeks with erlotinib and showed no significant pharmacokinetic interactions but an inability to give full doses of both drugs. Recommended phase II doses were 60 to 70 mg/m^2 docetaxel every 3 weeks and 100 mg erlotinib orally daily (21) or 200 mg erlotinib on days 2 to 16 every 3 weeks (22).

In this study, we aimed to define the maximum tolerated dose (MTD) of weekly docetaxel in combination with erlotinib and to analyze the pharmacokinetics, safety, and tolerability of this regimen in patients with taxane-naive malignancies. The pharmacokinetics of docetaxel and erlotinib was done after

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Table 1. Characteristics of 25 enrolled patients

Characteristic	Number	%
Age, median (range)	56 (34-76)	
Sex		
Female	7	28
Male	18	72
Race		
Caucasian	24	96
African-American	1	4
Hispanic	0	0
ECOG performance status		
0	21	84
1	4	16
2	0	0
Tumor type		
Non–small cell lung	4	16
Esophageal	4	16
Pancreatic	4	16
Transitional cell	3	12
Unknown primary	3	12
Cholangiocarcinoma	2	8
Gastric	1	4
Thyroid	1	4
Hepatocellular	1	4
Prostate	1	4
Sarcoma	1	4
Previous treatment		
Chemotherapy		48
1 regimen	7	28
≥2 regimens	5	20
Radiotherapy	14	56
Surgery	11	44
None	5	20

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

28 days of continuous erlotinib dosing, when the latter was at steady state. The pharmacokinetic data were to be compared with historical controls.

Materials and Methods

Patients with advanced solid tumors were eligible if they received no more than one previous chemotherapy regimen for metastatic disease, had an Eastern Cooperative Oncology Group performance status ≤2, and had adequate hematopoietic function [aspartate aminotransferase/alanine aminotransferase ≤1.5× upper limit of normal (ULN) if alkaline phosphatase ≤ ULN or alkaline phosphatase ≤4× ULN if aspartate aminotransferase/alanine aminotransferase ≤ ULN, bilirubin ≤ ULN and creatinine ≤1.5× ULN or creatinine clearance >60 mL/min/m^2]. Patients were excluded from the study if they had chemotherapy within 4 weeks, radiation therapy within 2 weeks, symptomatic brain metastases or requiring corticosteroids, or prior taxane exposure except adjuvant taxanes completed more than 12 months before. All participating patients signed an informed consent form reviewed and approved by the Indiana University Review Board.

Study design. This was a single-center, phase I, dose-escalation study to establish the MTD of weekly docetaxel combined with daily erlotinib. Erlotinib (150 mg) was taken orally daily. Docetaxel was given on days 1, 8, and 15 of each 28-day cycle and infused over 30 min. Premedication for weekly docetaxel consisted of 4 mg dexamethasone orally for three doses beginning the day before, morning of, and the day after docetaxel infusion. Docetaxel doses started at 20 mg/m^2 and escalated to 25, 30, and 35 mg/m^2 in cohorts of three patients per level. A standard "3 + 3" design was used. If one of three patients experienced dose-limiting toxicity (DLT), an additional three patients were accrued to that dose level. If two or more patients in a cohort experienced DLT, then the previous dose was considered the MTD and dose escalation was terminated. Additional 7 patients were entered to ensure 10 patients were treated at the MTD. Patients were to be treated for up to 6 cycles of docetaxel and 12 cycles of erlotinib. The pharmacokinetic profiles of docetaxel and erlotinib were defined on cycle 2, day 1.

Definition of DLT and dose modifications. DLT was defined as any of the following events during the first cycle: grade 4 thrombocytopenia, grade 4 neutropenia lasting more than 7 days, grade 3 or 4 febrile neutropenia, any grade 3/4 nonhematologic toxicity related to the combination therapy except nausea/vomiting or alopecia, or missing two doses of docetaxel per dosing guidelines due to failure to recover hematologic counts. Dose reductions were based on hematologic and nonhematologic toxicities. No more than two dose modifications were allowed for any one patient. Treatment was discontinued for disease progression, unacceptable toxicity, therapy delay for more than 3 weeks because of any toxicity, and withdrawal of consent. All patients who received at least one dose of docetaxel and erlotinib were evaluable for safety. Response to therapy was assessed by using the Response Evaluation Criteria in Solid Tumors criteria (23).

Pharmacokinetics. Plasma samples for pharmacokinetic analysis were obtained on cycle 2, day 1 for docetaxel and erlotinib (OSI-774) and its metabolite, OSI-420. Erlotinib and docetaxel administrations were started at the same time and pharmacokinetic samples were collected before treatment, at the end of the docetaxel infusion, and then 15 min, 45 min, 2 h, 3 h, 6.5 h, 8 h, and 24 h after the end of the docetaxel infusion. Erlotinib and its *O*-demethylated metabolite, OSI-420, concentrations were extracted from plasma under basic conditions with hexane/ethyl acetate (50:50). Then, erlotinib and OSI-420 were quantified by liquid chromatography-tandem mass spectrometry using midazolam as the internal standard (24). The standard curve concentrations ranged from 10 to 5,000 ng/mL. The pharmacokinetics of erlotinib concentrations was done using noncompartmental methods with WinNonlin version 5.01. Docetaxel concentrations were determined using a validated liquid chromatography-mass spectrometry assay in atmospheric pressure chemical ionization mode. The assay was linear from 1 to 1,000 ng/mL using 1 mL plasma. The coefficient of variation for the low control (75 ng/mL) and the high control (500 ng/mL) was <10%. The assay was done as previously reported, with the exception that paclitaxel was used as the internal standard and docetaxel was the analyte of interest (25). ADAPT II software was used for docetaxel pharmacokinetic data analysis (Biomedical Simulations Resource; ref. 26). A three-compartment model was fit to each patient data using a Bayesian algorithm as implemented in ADAPT II software. Prior variable distributions were derived from the literature (27).

Statistical analysis. Acceptable toxicity of this regimen was considered if none of three patients, or less than one or one of six patients had DLT. Based on the binomial distribution for toxicity occurrence, there was at most a 17% chance of escalating to the next dose level when the true toxicity rate exceeded 50%. With six patients in a cohort, there was at least a 74% chance of observing any toxicity with a true rate of >20%. All toxicity was summarized in a tabular manner for all encountered events. The MTD or the highest dose tested was to be expanded to 10 patients.

Results

Patient characteristics. Characteristics of the 25 patients enrolled in this study are summarized in Table 1. The median time on study was three cycles (12 weeks). Five patients completed all 6 cycles of docetaxel and erlotinib, and three patients continued erlotinib for 8, 10, and 12 cycles, respectively. Four patients discontinued therapy before completing the

first cycle: one patient due to DLT (grade 3 enterocolitis), two patients due to bilirubin fluctuation due to Gilbert's syndrome and inability to dose per protocol, and one patient due to dysphagia from an esophageal stricture due to disease progression. Twenty-two patients are evaluable for safety and 21 patients are evaluable for efficacy and pharmacokinetics.

Toxicity. The MTD of docetaxel in combination with erlotinib was not reached in this study. Treatment summary and DLT are provided in Table 2. One of six patients at dose level 25 mg/m^2 experienced a DLT with grade 3 diarrhea, nausea, and vomiting on cycle 1, day 10 and was hospitalized on cycle 1, day 14. The last docetaxel dose was on cycle 1, day 8, and the last erlotinib dose was on cycle 1, day 14. This patient with metastatic bladder cancer and treated with two prior chemotherapy regimens and pelvic radiotherapy was diagnosed with grade 3 enterocolitis and with partial small bowel obstruction and small amount of free air on abdominal computed tomography scan. Diarrhea improved with diphenoxylate/atropine and i.v. fluids. A surgical evaluation considered that the patient had a sigmoid perforation possibly due to metastatic tumor implants, but because of clinical improvement, the patient declined surgical exploration. This DLT was attributed to both docetaxel and erlotinib and the patient discontinued the study on cycle 1, day 14. The patient recovered without surgery and was discharged home in stable condition 2 days after study discontinuation. One patient in the 25 mg/m^2 docetaxel cohort was diagnosed with grade 2 interstitial pneumonitis on cycle 3, day 26, which responded to treatment with steroids. The last docetaxel dose was on cycle 3, day 15, and the last erlotinib dose was on cycle 3, day 22. The patient discontinued the study on cycle 3, day 26 but died 23 days later due to progressive metastatic pancreatic cancer. The interstitial lung disease was attributed to the combination of erlotinib and docetaxel.

No patients treated with 20 to 30 mg/m^2 docetaxel required dose reductions, but 6 of 10 patients in the 35 mg/m^2 cohort needed dose reductions to 30 mg/m^2 beyond cycle 1 as follows: on cycle 2, day 1, three patients due to grade 3 neutropenia (including a patient dose reduced again on cycle 3, day 1 to 25 mg/m^2 due to grade 2 infection) and one patient due to grade 3 mucositis; on cycle 3, day 1, one patient dose reduced due to grade 1 hyperbilirubinemia; and on cycle 4, day 1, one patient dose reduced due to persistent grade 2 diarrhea and abdominal cramping. In addition, one patient discontinued docetaxel on cycle 5, day 15 due to grade 1 epiphora (eye tearing; Table 2). One of three patients in the 30 mg/m^2 cohort received six cycles of docetaxel with no dose reductions, and two patients had disease progression after two cycles. Among six patients who required dose reductions from 35 to 30 mg/m^2, four patients received only one additional cycle due to disease progression, one patient (grade 3 diarrhea at 35 mg/m^2) received three additional cycles of therapy, and one patient (grade 1 hyperbilirubinemia at 35 mg/m^2) received four additional cycles at 30 mg/m^2, respectively, with no recurrence of prior toxicity. Thus, in the absence of disease progression, cumulative dosing at 30 mg/m^2 was tolerable, justifying this as the recommended dose for phase II testing.

Erlotinib was dose reduced in two patients in the 25 mg/m^2 cohort due to grade 2 conjunctivitis (cycle 3, day 15) and grade 2 mucositis (cycle 2, day 15), respectively.

Hematologic toxicity was uncommon, except for grade 3 neutropenia during the cycle 1 in 3 of 10 patients in the 35 mg/m^2 dose level, which has not recurred after docetaxel dose reduction in subsequent cycles, and one of the non-evaluable patients (due to Gilbert's) had grade 4 neutropenia while off study (Table 3).

Nonhematologic drug-related adverse events are summarized in Table 3. The most common toxicities were diarrhea, rash,

Table 2. Treatment summary, DLTs (N = 22 patients evaluable)

Docetaxel dose level (mg/m^2)	No. cycles/patient		No. DLTs	Dose reductions/discontinuations for AEs				
	Docetaxel, median (range)	Erlotinib, median (range)		Drug	1st day DR	DC	Off study	Reason for DR/DC
20 (n = 3)	4 (2-4)	4 (2-4)	0/3	D, E	—	C4D1	C4D8	gr 3 thrombocytopenia
25 (n = 6)	3 (1-6)	3 (1-6)	1/6	D, E	—	C1D15	C1D15	gr 3 enterocolitis
				E	C2D15		C4D15	gr 2 mucositis
				E	C3D15		C6D15	gr 2 conjunctivitis
				E			C3D26	gr 2 pneumonitis
30 (n = 3)	2 (2-6)	2 (2-6)	0/3		—			
35 (n = 10)	3 (2-6)	3 (2-12)	0/10	D	—	C5D15	C12D28	gr 1 eye tearing
				D	—	C6D15	C6D23	gr 3 neuropathy
				D	C2D1	C2D15	C3D1	gr 3 neutropenia
				D	C2D1	C2D15	C3D1	gr 3 neutropenia
				D	C2D1	C3D15	C3D15	gr 3 neutropenia
					C3D1*	C3D15	C3D15	gr 2 infection
				D	C4D1	C6D15	C9D1	gr 3 diarrhea
				D	C3D1	C6D15	C10D28	gr 1 hyperbilirubinemia
				D	C2D1	C3D1	C3D1	gr 3 mucositis

Abbreviations: AE, adverse event; D, docetaxel; E, erlotinib; DR, dose reductions; DC, discontinuation; gr, grade toxicity; C4D1, cycle 4, day 1; C4D8, cycle 4, day 8; C1D15, cycle 1, day 15; C2D15, cycle 2, day 15; C4D15, cycle 4, day 15; C3D15, cycle 3, day 15; C6D15, cycle 6, day 15; C3D26, cycle 3, day 26; C5D15, cycle 5, day 15; C12D28, cycle 12, day 28; C6D23, cycle 6, day 23; C2D1, cycle 2, day 1; C3D1, cycle 3, day 1; C4D1, cycle 4, day 1; C9D1, cycle 9, day 1; C10D28, cycle 10, day 28.
*One patient had two docetaxel dose reductions.

and mucositis, but most cases were grade 1 or 2. Grade 3/4 nonhematologic adverse events occurring in more than one patient were diarrhea (three patients), mucositis (two patients), and nausea, vomiting, dyspnea, and neuropathy (one patient each).

Table 3. Summary of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0)

	Docetaxel dose			
	20 mg/m² (*n* = 3)	25 mg/m² (*n* = 6)	30 mg/m² (*n* = 3)	35 mg/m² (*n* = 10)
Hematologic adverse events				
Neutropenia				
Grade 1	0	0	0	0
Grade 2	0	1	0	0
Grade 3	0	0	0	3
Grade 4	0	0	0	1
Thrombocytopenia				
Grade 1	0	0	0	1
Grade 2	0	1	0	0
Grade 3	1	1	0	0
Grade 4	0	0	0	0
Anemia				
Grade 1-4	0	0	0	0
Nonhematologic adverse events				
Fatigue				
Grade 1/2	1	1	0	6
Grade 3	0	0	0	0
Nausea				
Grade 1/2	2	1	1	5
Grade 3	0	1	0	0
Vomiting				
Grade 1/2	1	0	0	1
Grade 3	0	1	0	0
Diarrhea				
Grade 1/2	3	4	3	8
Grade 3	0	1	0	2
Enterocolitis				
Grade 1/2	0	0	0	0
Grade 3	0	1	0	0
Oral mucositis				
Grade 1/2	1	2	2	8
Grade 3	0	0	0	2
Rash				
Grade 1/2	3	4	3	10
Grade 3	0	0	0	0
Infection				
Grade 1/2	0	0	0	2
Grade 3	0	0	0	0
Eye tearing				
Grade 1/2	0	1	0	3
Grade 3	0	0	0	0
Interstitial lung disease				
Grade 1/2	0	1	0	0
Grade 3	0	0	0	0
Dyspnea				
Grade 1/2	0	1	0	3
Grade 3	0	1	0	0
Neuropathy				
Grade 1/2	0	1	0	3
Grade 3	0	0	0	1
Nail changes				
Grade 1/2	0	0	0	4
Grade 3	0	0	0	0
Cracked skin				
Grade 1/2	0	1	0	4
Grade 3	0	0	0	0

Recommended phase II dose. We did not define the dose level of weekly docetaxel in combination with erlotinib with excess DLT during cycle 1 per protocol definition. However, because a substantial proportion of patients required docetaxel dose reduction to 30 mg/m^2 for ongoing dosing beyond cycle 1, and this dose proved tolerable with repetitive dosing, our recommendation for phase II dosing will be 30 mg/m^2 docetaxel weekly for 3 of 4 weeks and 150 mg erlotinib daily.

Pharmacokinetics. Twenty-one patients had pharmacokinetic studies completed. The mean docetaxel clearance was 61.7 L/h (range, 30.6-112.3), the mean volume of distribution was 8.0 L (range, 3.8-13.1), and the area under the plasma concentration-time curve (AUC) from time 0 to 24 h (AUC_{0-24}) was 0.986 μg·h/mL (Table 4). A plot of plasma concentration-time curves for docetaxel for each dose level is shown in Fig. 1A. The mean erlotinib (OSI-774) clearance (±SD) was 8.16 ± 4.05 L/h with AUC_{0-24} of 24.08 ± 13.77 μg·h/mL and maximum plasma concentration (C_{max}) of 1,381 ± 692.8 ng/mL. The OSI-420 had an AUC_{0-24} of 3.15 ± 2.36 μg·h/mL and C_{max} of 190.5 ± 122 ng/mL (Table 5). A plot of average (±SD) erlotinib and OSI-420 concentrations is shown in Fig. 1B.

Correlation of acneiform skin rash to plasma erlotinib exposure. The incidence and severity of rash (grade 0/1 versus grade ≥2) were analyzed in 21 patients and correlated with erlotinib pharmacokinetics. We noted a significant correlation between rash grade and the erlotinib plasma exposure. Specifically, patients with acneiform rash that was grade ≥2 (n = 12) had a higher AUC_{0-24} (30.927 μg·h/mL) than patients with grade 0/1 rash (n = 9; AUC_{0-24}, 14.959 μg·h/mL; P = 0.003).

Antitumor activity. Twenty-one patients were evaluable for tumor response according to Response Evaluation Criteria in Solid Tumors criteria. Four patients (19%) obtained confirmed partial responses to therapy. One patient with hepatocellular carcinoma who previously underwent partial hepatectomy relapsed 5 months later with lung metastases and an α-fetoprotein level of 2,279. This patient obtained a complete response after two cycles of therapy (35 mg/m^2 docetaxel) and is alive with no evidence of disease more than 36 months since commencing protocol therapy (α-fetoprotein normalized at 3.4). Two patients with cholangiocarcinoma had tumor response: one patient treated with 35 mg/m^2 docetaxel showed a partial response that lasted for 8 months and another patient treated with 25 mg/m^2 docetaxel had a minor response (20% decrease in tumor) lasting 2 months; this patient was removed from study due to biliary stent malfunction preventing redosing per protocol due to bilirubin elevation. One patient with prostate cancer with liver and soft tissue metastases treated with 35 mg/m^2 docetaxel obtained a partial response for 8 months. A patient with non–small cell lung cancer and prior history of treated brain metastases in the 25 mg/m^2 cohort had a partial response of an isolated hilar mass, which lasted for 6 months. This patient later received chest radiotherapy and has been with no evidence of disease for more than 26 months. All responses were documented after two cycles of therapy. Six patients (28%; two non–small cell lung cancer, one cholangiocarcinoma, one gastric, one bladder, and one colon) had stable disease lasting 2 to 6 months. Responding and stable disease patients received a median of 6 cycles of docetaxel and erlotinib combination therapy (range, 4-6 cycles of docetaxel and 4-12 cycles of erlotinib).

Table 4. Pharmacokinetic variables for docetaxel on day 29 (cycle 2, day 1) versus day 1 historical controls

	C_{max} (ng/mL), mean ± SD	AUC_{0-24} (μg·h/mL), mean ± SD	Cl (L/h/m^2), mean ± SD	Cl (L/h), mean (range)
Docetaxel (35 mg/m^2), day 29 (current study)	1,539 ± 397.5	1.037 ± 0.39	30.56 ± 9.33	61.7 (30.6-112.3)
Docetaxel (35 mg/m^2), day 1 (29)	1,850 ± 730	1.32 ± 0.42	29.1 ± 10.2	NA

Abbreviations: Cl, clearance determined by dividing the dose by the AUC; NA, not available.

Discussion

Results of this phase I study show that the combination of daily erlotinib and weekly docetaxel can be tolerated, but with repetitive dosing at 35 mg/m^2 of docetaxel, most patients experienced drug-related toxicities, especially neutropenia, diarrhea, and mucositis, prompting docetaxel dose reductions to 30 mg/m^2 beyond the first cycle (Table 2). All three patients who developed grade 3 neutropenia had received chemotherapy with one or more prior regimens, and two of these three patients also had prior radiotherapy. Only one other patient in this cohort was treated with prior chemotherapy and did not require dose reductions for myelosuppression, suggesting that prior treatment with chemotherapy may have been a predisposing factor for myelosuppression from the docetaxel-erlotinib combination. The one patient who required docetaxel dose reduction for diarrhea with no associated myelosuppression on cycle 4, day 1 had prior pelvic radiotherapy and hormonal therapy for prostate cancer. Patients treated with 30 mg/m^2 tolerated repetitive dosing for up to six cycles, with no major toxicity. Overall, the most common adverse events were gastrointestinal and dermatologic and were seen across dose levels, but more grade 3/4 toxicities occurred at 35 mg/m^2 docetaxel dose level. Although rash was commonly seen and could be attributed to erlotinib, no patient had grade 3 or 4 skin toxicity, and its incidence was not higher than expected with single-agent erlotinib (12).

The pharmacokinetic variables of docetaxel on cycle 2, day 1 were similar to those reported for single-agent docetaxel given every 3 weeks at doses of 60 to 115 mg/m^2 (27, 28) or weekly at 35 mg/m^2 (Table 4; ref. 29). Four patients treated with 35 mg/m^2 docetaxel were dose reduced to 30 mg/m^2 on cycle 2, day 1. Their pharmacokinetic variables were similar compared with the patients who received full dose docetaxel (clearance, 58.67 versus 68.11 L/h; volume of distribution, 3.4 versus 3.75 L/m^2; and AUC_{0-24}, 0.99 versus 1.00 μg·h/mL). Erlotinib pharmacokinetic variables indicate similar C_{max} [1,381 ng/mL (this study) versus 1,136-1,238 ng/mL (historical controls)] and clearance [8.16 L/h (this study) versus 10.11 L/h (controls)] as other phase I studies with single-agent erlotinib (Table 5; refs. 30, 31). All patients achieved erlotinib concentration values in excess of 500 ng/mL, which is the concentration associated with antitumor activity in preclinical models. Due to no appreciable difference from historical controls, these data suggest no effect on the clearance of either drug with the combination of docetaxel and erlotinib.

Although tumor evaluation was not the primary objective of this study, five confirmed objective responses were seen

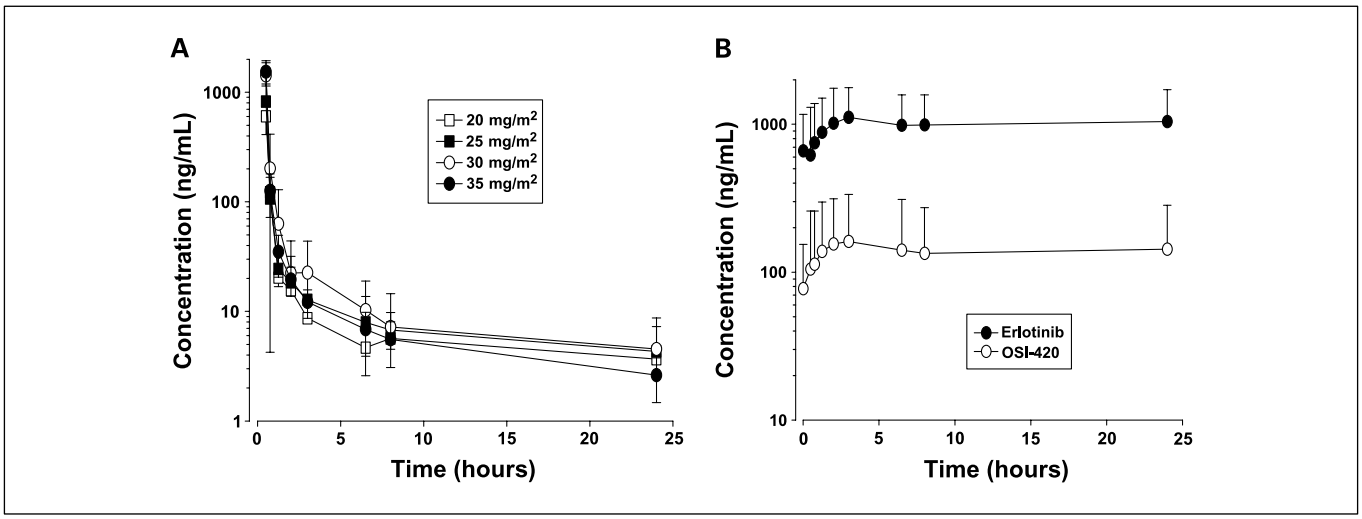

Fig. 1. *A,* plasma concentration-time profile for docetaxel at 20 mg/m^2 (□), 25 mg/m^2 (■), 30 mg/m^2 (○), and 35 mg/m^2 (●) on cycle 2, day 1. *B,* plasma concentration-time profile for erlotinib (OSI-774; ●) and OSI-420 (○) on cycle 2, day 1.

Table 5. Pharmacokinetic variables for erlotinib (OSI-774) and OSI-420 on day 29 (cycle 2, day 1) versus day 1 single-agent erlotinib historical controls

	C_{max} (ng/mL), mean ± SD	AUC_{0-24} (μg·h/mL), mean ± SD	Cl/F (L/h), mean ± SD
OSI-774 (150 mg/d), day 29 (current study)	1,381 ± 692.8	24.08 ± 13.77	8.16 ± 4.05
OSI-774 (150 mg/d), day 1 arm B (31)	1,136 ± 865	16.51 ± 11.02	10.11 ± 12.51
OSI-774 (150 mg/d), day 1 arm C (31)	1,238 ± 598	18.61 ± 5.99	NA
OSI-420, day 29 (current study)	190.5 ± 122	3.15 ± 2.36	NA
OSI-420, day 1 (31)	85 ± 38	1.69 ± 1.42	NA

Abbreviation: Cl/F, oral clearance determined by dividing the dose by the AUC.

(hepatocellular carcinoma, cholangiocarcinoma, non–small cell lung cancer, and prostate cancer). Advanced-stage hepatocellular carcinoma and biliary malignancies have a dismal prognosis, and neither chemotherapy nor biological therapies prolong median survival beyond 1 year. One patient with hepatocellular carcinoma obtained a complete response lasting 36+ months, and two patients with cholangiocarcinoma obtained responses, one with partial response for 8 months. The benefit of adding EGFR tyrosine kinase inhibitors to chemotherapy was initially doubted based on two platinum doublet trials with or without an EGFR tyrosine kinase inhibitor, which yielded negative results in non–small cell lung cancer (32–34). However, a small but meaningful benefit was seen in some patients when gemcitabine was combined with erlotinib in pancreatic cancer (13). The sequence-dependent antiproliferative effects of cytotoxic drugs and EGFR inhibitors may be important, as synergistic activity was seen preclinically when chemotherapy was followed by treatment with EGFR antagonists (35). Although not noticed in our and other studies, another possibility for the discrepancy between the preclinical and clinical data is that of a drug-drug interaction resulting in decreased exposure to one or more of the agents.

In conclusion, this study showed that weekly docetaxel can be combined with daily erlotinib, but 35 mg/m^2 docetaxel is intolerable with repetitive dosing beyond the first cycle. Although no MTD was reached in cycle 1 with 35 mg/m^2 docetaxel, the recommended phase II dose of weekly docetaxel is 30 mg/m^2 when combined with 150 mg of daily erlotinib. Combined dosing of docetaxel and erlotinib did not seem to alter the pharmacokinetics of either drug. The antitumor activity of this regimen provides the rationale for further testing in phase II studies of various solid tumors, including hepatobiliary malignancies.

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